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EXAMINER	
RAO, SAVITHA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,288	YI, XIANGHUI	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-12,14-19, 22-25 and 26-29* is/are pending in the application.

4a) Of the above claim(s) *7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6, 11-12, 14-19, 22-25 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4-12, 14-19, 22-25 and 27-29 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on November 12th 2009 is acknowledged. Claim 6 and 29 are amended and claim 26 is cancelled. Claims 7-10 are withdrawn from consideration as being drawn to a non-elected invention, Claims 4-6, 11-12, 14-19, 22-25 and 27-29 are under consideration in the instant office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/12/2009 has been entered.

Applicants' arguments, and the documents (Exhibit A, B and C) filed 11/12/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

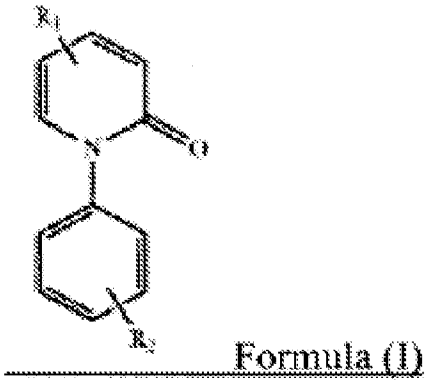
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 4, 6, 11-12, 14-18 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin (US 6090822, referenced in the instant IDS)in view of Worbel et al (J. Med. Chem., 1989, Volume 32(11): 2493-3000, abstract) and Patani et al (Chemical Reviews, 1996, Vol.96 (8), pages 3147-3176) as evidenced by Ansel et al (Pharmaceutical dosage forms and drug delivery systems, Seventh edition, pages 87-92, Copyright 1999, reference already of record)

Instant claim 4-6 and 11-12, 14-19 is drawn towards a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of the compound of formula 1



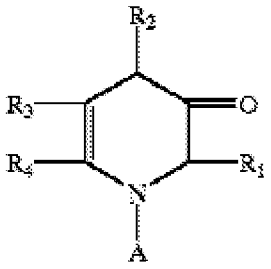
Formula (I)

Where R1 is methyl at position 5 and R2 is hydroxy at position 4 (instant claims 11 and 12).

Margolin teaches drugs having pharmacological properties which are useful in the treatment of disorders caused by enhanced proliferation and enhanced biosynthesis caused by cytokine growth factors in humans, such drugs including as active ingredients one or more N-substituted 2-(1H) pyridone(s) and/or N-substituted 3-(1H) pyridones (abstract, col.1, line 66 to col.2 12). Margolin teaches that 5-methyl -1-phenyl-2-(1H)-pyridone, "pirfenidone" and related substances inhibit the proliferation and activating actions of cytokine growth factors and as a result, prevent or correct the lesions' generated in conditions such as allergy, auto-immunity, immunosuppression, fibrotic lesions, infections of virus origin such as herpes, tissue injuries caused by bacterial or fungal infections, tissue injury due to trauma, etc. and Margolin additionally teaches that these drugs inhibit the pathogenic actions in a pharmacological manner at doses which are much smaller than those which produce toxic effect in in vitro tissue cultures and living animals and humans (col.2, lines 26-41). Margolin teaches N-

substituted 3-(1H) pyridones useful in his inventions and exemplifies compounds of formula (col. 7, lines 1-16)

The general structural formual for the 3 pyridones is:



where: R2 or R3=alkyl group or hydrogen, as above; A is phenyl, thienyl, etc., or other aryl. R1 and R4 are hydrogen.

Examples of the 2 and 3 pyridones include:

5-Methyl-1-(3-nitrophenyl-2)-(1H) pyridone

5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone

Compound 5-Methyl -1-(4'-methoxyphenyl-2-(1H)-pyridone taught by Margolin is structurally similar to the instantly claimed compound except for the methoxy substitution on the phenyl ring instead of the hydroxy or methylthio or ethylthio substitution of the instantly claimed compound. Additionally Margolin teaches examples of medical preparations of the compound pirfenidone useful in his preparations which include (1) capsules (2) tablets (3) powders (4) granules (5) syrups (6) injectable (7) cream (8) ointment (9) inhalation (10) eye drop (11) suppositories (12) pills, etc. and indicates that the preparations preferred among these are the capsules, injections cream and ointments (col. 8, lines 30-34). Margolin teaches the effective dosages to be in the ranges from about 10-75 mg/kg body weight per day in divided (col.8,lihes 26-29). Accordingly, Margolin provides one of ordinary skill in the art motivation to synthesize N-

substituted pyridones with different substitution on the phenyl group and prepare pharmaceutical compositions.

Margolin does not teach N-substituted pyridone where in the substitution in position 4" of the phenyl group is either hydroxy or methylthio or ethylthio.

However, Compound 5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone taught by Margolin is an obvious variant of the instantly claimed compound.

The following obvious modifications for 5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone of Margolin occurs in the 4'' methoxy substitution on the phenyl ring attached to the pyridone moiety, I

1. Substitution of hydroxy instead of the methoxy group.

2. Substitution of methylthio or ethylthio group in place of the methoxy group.

With regards to the H v. -CH3 substitution in the methoxy group,. Hydrogen and methyl are deemed obvious variants. In re Henze, 85 USPQ 261 (1950), In re Wood, 199 USPQ 137 (CCPA 1978), and In re Lohr, 137 USPQ 548,549 (CCPA 1963) and the interchange of alkyl and hydrogen is obvious in and of itself, Ex parte Blustone 135, USPQ 199. Accordingly, it would have been obvious for one of ordinary skill in the art to substitute hydrogen for the methyl group of the methoxy function attached at the 4' position of the phenyl group in the compound taught above to obtain a hydroxy derivative.

With regards to the substitution of the methoxy group with methylthio group or ethylthio group, Worbel et al teaches methoxy group as a bioisosteres of the methylthio substituent (line 10-11 of the abstract) in their development of aldose reductase

inhibitors. Patani et al. teaches that a lead compound with the desired pharmacological activity may have associated with it undesirable side effect, characteristics that limit its bioavailability or structural features which adversely influence its metabolism from the body and bioisosterism is one approach used by the medicinal chemist for the rational modification of the lead compound into safer and more clinically effective agents (page 3147, left col. 1st paragraph to right col., 1st paragraph). Accordingly, with 5-Methyl-1-(4'-methoxyphenyl)-2-(1H) compound taught by Margolin as the lead compound it would have been obvious to an ordinarily skilled artisan to substitute the methoxy with the methyl thio group in developing a structural activity basis of these compounds. In addition methyl and ethyl groups are adjacent homologues and it is noted that adjacent homologues are considered to be obvious absent unexpected results, *In re Henze*, 85 USPW 261, 263. As such replacement of methoxy group of the compounds taught by Margolin with the methylthio group or ethyl thio group would have been obvious to an ordinarily skilled artisan.

MPEP 2144.08.II.A.4(c) states, "... consider teachings of a preferred species within the genus. If such a species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties." To those skilled in the chemical art, one homologue is not an advance over an adjacent member of a homologous series. The reason for this is that one of ordinary skill, knowing the properties of one member of series, would know what properties to expect in adjacent members

With respect to the pharmaceutical composition comprising a pharmaceutically acceptable excipient as recited in instant claim 1, formulation of different pharmaceutical compositions as taught by Margolin would require that the compound be combined with different excipients suitable for formulation. For example, formulation into a capsule would require the drug to be mixed with suitable carriers or diluent and in addition would include preservatives, colorants, stabilizers, opaquant etc. Formulation of the compound in the ointment as taught by Margolin would require the ointment to have ointment base. Formulation of drugs into various dosage forms is well known in the pharmaceutical arts and Margolin's teachings that compounds of N-substituted pyridones are easily formulated into capsule or ointment form provides ample motivation to an ordinarily skilled artisan in pharmaceutical arts to develop different dosage forms of the hydroxy, or methylthio or ethylthio phenyl substituted compounds using suitable excipients. Ansel et al used here as evidentiary reference teaches different types of excipients or pharmaceutical ingredients required to prepare a drug substance into a final dosage form. Ansel teaches the use of solvents to dissolve the drug substance, flavorants to make the product more palatable, colorants to enhance product appeal, preservative to prevent microbial growth and stabilizers such as antioxidants to prevent drug decomposition, diluents or fillers to increase the bulk of the formulation, binders to cause the adhesion of the powdered drug, lubricants to assist smooth tabletting process, disintegrating agents to promote tablet break up after administration and coatings to improve stability. Ansel et al teaches that for each dosage form the pharmaceutic ingredient establish the primary features of the product and contribute to

the physical form, texture, stability, taste and overall appearance (page 87 right col. 3rd paragraph).

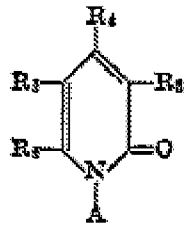
The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. It would have been *prima facie* obvious to the skilled artisan to combine the teachings Margolin and Worbel et al to prepare 5-methyl-1-phenyl-2(IH) pyridine with different substituents at the 4' position of the phenyl moiety such as hydroxy, methylthio or ethylthio. A compound and pharmaceutical compositions with no phenyl substitution (5-methyl-1-phenyl-2(1-H or pirfenidone) and the one with methoxy substituent on position 4' of the phenyl ring (5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridine) are already taught in the art the fact that they possess anti-fibrotic activity has already been taught. Formulation of drugs into tablets or other dosage forms by combining different excipients imparting different functions to the dosage form is well known in the art as taught by Ansel et al. Accordingly, In view of the close structural similarity between the claimed compound in the instant pharmaceutical composition and the compound taught by both Margolin, one of ordinary skilled in the art would have been motivated, from the disclosure in the prior art, to make the modifications and formulate them into pharmaceutical compositions required to arrive at the instant invention with reasonable expectation of success for obtaining a compound with the same utility. The motivation to make the change would be to make additional

compounds for the quoted purpose, which is to treat disorder caused by enhanced proliferation and enhanced biosynthesis caused by cytokine growth factor.

Claim 5, 19, 22-25 and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin, Patani et al. and Worbel et al. applied to claims 4, 6, 11-12, 14-18 and 27 above, and further in view of Gadeker (US3839346, already of record)Ansel et al ((Pharmaceutical dosage forms and drug delivery systems, Seventh edition, pages 87-92, Copyright 1999, reference already of record)

Margolin, Patani et al and Worbel et al teach as discussed supra and are applied here in the same manner. The cited references do not teach the details of the excipients in the pharmaceutical compositions as instantly claimed, do not teach the formulation being a slow release dosage form and do not precisely teach the wherein the compound comprises 0.01-99% or 0.1-90% of the composition on the basis of the total weight.

However, Gadekar teaches Novel analgesic compositions containing as the active ingredient the compound 5-methyl-1-phenyl-2(1-H) pyridone (abstract). Gadekar also describes methods of making related pyridones having the formula



II

wherein A is an aromatic group; R_3, R_4, R_5 and R_6 are individually each hydrogen, alkyl, aryl or substituted aryl;

(col. 3, lines 14-27) and in example 3 Gadekar teaches the synthesis of 5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone taught by Margolin above (col.5, lines 69-75).

Gadekar teaches pharmaceutical composition of 5-methyl-1-phenyl-2(1-H)pyridone formulated together with a pharmaceutically acceptable carrier, solid carrier, diluent or a gaseous carrier to provide pharmaceutical compositions in forms suitable for therapeutic administration (col.2, lines 42-49). Gadekar teaches that the solid carriers are useful in formulation of dosage forms such as pills, tablets , powders or cachets for immediate or sustained release and may include flavors or therapeutic adjutants , the liquid carrier can provide flavorful vehicle for oral administration or may be adjusted to tonicity to be used in injectable preparations.(col.2, lines 50-60). Additionally, Gadekar teaches that the standard pharmaceutically acceptable carriers normally used in such pharmaceutical formulations can be utilized in formulating the aforementioned compositions of his invention (col.3, lines 9-13) . Gadekar teaches therapeutic dosage form of 5-methyl-1-phenyl-2(1-H)pyridone which comprises about 100 mg -500 mg of the compound with other excipients in a tablet formulation and about 100 mg in a therapeutic solution formulations with other excipients. In the therapeutic solution formulation the composition comprises about 10% in weight of the drug. This compound taught by Gadekar is identical to one of the compounds taught by Margolin and as such provides ample suggestion to an ordinarily skilled artisan that such structurally similar compounds can be formulated in the manner similar to that of Gadekar.

Ansel et al teaches different types of excipients or pharmaceutical ingredients required to prepare a drug substance into a final dosage form. Ansel teaches the use of solvents to dissolve the drug substance, flavorants to make the product more palatable, colorants to enhance product appeal, preservative to prevent microbial growth and stabilizers such as antioxidants to prevent drug decomposition, diluents or fillers to increase the bulk of the formulation, binders to cause the adhesion of the powdered drug, lubricants to assist smooth tabletting process, disintegrating agents to promote tablet break up after administration and coatings to improve stability. Ansel et al teaches that for each dosage form the pharmaceutical ingredient establish the primary features of the product and contribute to the physical form, texture, stability, taste and overall appearance (page 87 right col. 3rd paragraph). In Table 3.3 (pages 88-91) Ansel et al. exemplifies several components used for each of the category above. for example Ansel et al. teaches ascorbic acid, butylated hydroxyanisole (BHA) and butylated hydroxytoluene(BHT) as antioxidants (page 88), Mineral oil, alcohol, purified water, sterile water, corn oil, peanut oil etc as examples to be used as solvents (page 90)., starch, Lactose, dibasic calcium phosphate, microcrystalline cellulose as diluents (page 90). Accordingly, Ansel et al provides one of ordinary skill in the art motivation to formulate compositions of drugs using one or more of the listed excipients.

Accordingly Gadekar and Ansel et al. provides motivation to one of ordinary skill in the art to prepare compositions of compounds structurally similar to pirfenidone using different pharmaceutical excipients in different dosage forms.

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. It would have been *prima facie* obvious to the skilled artisan to combine the teachings Margolin, Worbel et al., Patani et al., Gadekar and Ansel et al. to prepare 5-methyl-1-phenyl-2(IH) pyridine with different substituents at the 4' position of the phenyl moiety. Gadeker teaches formulations comprising 5-methyl-1-phenyl-(1H)-pyridone with different excipients in different dosage forms such as tablets, capsules, sustained release forms etc. Formulation of drugs into tablets or other dosage forms by combining different excipients imparting different functions to the dosage form is well known in the art as taught by Ansel et al. Accordingly, In view of the close structural similarity between the claimed compound in the instant pharmaceutical composition and the compound taught by both Margolin and Gadekar, one of ordinary skilled in the art would have been motivated to formulate instantly claimed compositions, in the expectation that the composition would possess activities similar to that displayed by the compounds taught by Margolin and Gadekar.

Response to applicant's arguments filed on 11/12/2009 :

In light of the new grounds of rejection above, the arguments submitted on 11/12/2009 which was for the previously submitted rejection is moot. However, with reference to the current rejection examiner responds to the applicant's arguments as follows:

Applicant traverses the above rejection with the following arguments:

(a) The prior art as a whole teaches away from a composition of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone since during prosecution of European patent # 0702551 the official document submitted by Margolin has data that 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone had a relative anti-fibrotic activity of 0.0 that is no anti-fibrotic activity at all.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive. First, examiner would first like to point out that instant claims are drawn towards pharmaceutical compositions and not towards the method of treatment of fibrosis. Second, the Margolin reference (US 6090822) used in the instant rejection teaches the compounds structurally similar to the instantly claimed compound to be used for the prevention and treatment of disorders caused by enhanced proliferation and enhanced biosynthesis of cytokine growth factors. These disorders include conditions such as allergy, infections of virus origins, and injuries due to bacterial infection or trauma. As such an ordinarily skilled artisan would be motivated to modify the structure of 5-Methyl-1-(4'-methodyphenyl)-2-(1H)-pyridone taught by Margolin to possess this activity by obvious substitution of hydroxy, methylthio or ethylthio at the 4' methoxy position of the compound to obtain structurally similar compounds which would possess similar or better therapeutic potential than the compounds taught by Margolin. The compounds may have activity and efficacy in other conditions not necessarily the fibrotic condition based on its activity to inhibit the pathogenesis of some of the other diseases taught by Margolin.

Conclusion

Claims 4-6 and 11-12, 14-19, 22-25 and 27-29 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614